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Laurence Gamelin

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LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK
600 SOUTH AVENUE WEST
WESTFIELD, NJ 07090

EXAMINER

KLINKEL, KORTNEY L

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/12/2009 has been entered.

Claims 1, 6, 11 and 13 have been amended. Claims 2-3 and 7-10 stand canceled. Claim 14 was newly added. Claims 1, 4-6 and 11-14 are pending in the instant Office action.

Withdrawn Claim Rejections

Claim Rejections - 35 USC § 112 1st paragraph

The rejection of claims 6 and 9-12 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the inhibition or prevention of neurotoxicity by administering oxaliplatin with calcium and magnesium; where the magnesium is dosed in a parenteral dosage form and the calcium is dosed in both an oral and a parenteral dosage form at a time prior to, after, during or in any sequence is withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-5, 12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 reads as follows:

A combination useful for administration in anticancer therapy, comprising oxaliplatin, injectable calcium and magnesium for administration both before and after oxaliplatin treatment and calcium in oral form for administration following oxaliplatin treatment.

First of all, it is unclear what is meant by the claimed "combination". It is unclear whether this claim is directed toward a composition, a kit or a method of treatment. This claim can reasonably be interpreted to be directed toward a composition comprising oxaliplatin, calcium and magnesium, and the intended use is that the composition is injected both before and after oxaliplatin treatment and calcium in oral form is intended to be administered following administration of the claimed composition. However, this claim can also be reasonably interpreted to be directed toward a kit having (1) oxaliplatin, (2) injectable calcium, (3) magnesium (note that it is also unclear if the magnesium is meant to be injectable as well), and (4) calcium in oral form. Additionally, it is unclear what is meant by the descriptors "injectable" and "oral form" with respect to calcium and/or magnesium. It is unclear if these words merely describe the intended use of the ingredients, or if they are meant to impart some sort of a structural limitation. If some sort of a structural limitation is meant to be imparted, it is unclear what form

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“injectable” and “oral form” intend to impart. It is noted that an injectable form of calcium could also be taken orally. Along these lines of reasoning, the claim can reasonably be interpreted to be directed to a method of treatment due to the “active step” limitations “for administration both before and after oxaliplatin treatment...” “calcium...for administration following oxaliplatin treatment.” It is unclear if these steps intend for the claim to be a method of administration/treatment type claim, or, as addressed above, if the claim is intended to be a composition or a kit. In an effort to expedite prosecution, the Examiner is interpreting claim 1 to be directed to a kit comprising (1) oxaliplatin, (2) injectable calcium, (3) magnesium (in any form), and (4) calcium in oral form.

Claims 4 and 5 recite the limitation “the calcium”. There is insufficient antecedent basis for this limitation in the claim. Claim 1, upon which claims 4 and 5 depend recites what appears to be two different types or forms of calcium (note that this point is unclear due to the rejection of claim 1 above under 112 2nd paragraph). Accordingly, it is unclear which calcium “the calcium” refers to and if both the injectable calcium and the calcium in oral form are of the salts recited in claim 4, or if only one or the other form of calcium is in the particular salt forms recited in claim 4. Claim 5 recites wherein part of “the calcium” is in injectable form and the other part is in oral form. As with claim 4, it is unclear what “the calcium” refers to. Please note also that with respect to claim 5, it is unclear how the limitation “wherein part of the calcium is in injectable form and the other part is in oral form” limits parent claim 1.

Claim 5 recites the limitation “said injectable magnesium salt”. There is insufficient antecedent basis for this limitation in the claim. Claims 1 and 4 upon which

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claim 5 depends make no mention of injectable magnesium salt. Note that it is unclear if the magnesium recited in claim 1, upon which claim 5 ultimately depends, is intended to be injectable or not.

Claim 12 recites the limitation "said injectable magnesium". There is insufficient antecedent basis for this limitation in the claim. Claim 5 upon which claim 12 depends recites "injectable magnesium salt" not "injectable magnesium". Please note also that it is unclear if the magnesium recited in claim 1, upon which claim 12 ultimately depends, is intended to be injectable or not.

Claim 14 recites the limitation "the calcium administered following treatment with oxaliplatin". It is unclear which calcium administered following treatment with oxaliplatin this claim refers to. Claim 6, upon which claim 14 ultimately depends from, requires that calcium and magnesium be administered both before and after treatment with oxaliplatin. Claim 13, upon which claim 14 directly depends recites the administration of calcium by the oral route following treatment with oxaliplatin. There are two different types of calcium being administered after treatment with oxaliplatin.

Claim Rejections - 35 USC § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 11, and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

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matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 6 and 13 have been amended to recite at least 1 g calcium and at least 1 g of magnesium and at least 1 g/day. There is no support in the instant specification for these limitations. The specification provides support for 1 g calcium and 1 g magnesium (see [0030]) and 1 g/day (see [0031]), but not for any amounts greater or less than these amounts.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Laine-Cessac et al. ("Acute Oxaliplatin Neurotoxicity Dramatically Improved with Intravenous Calcium and Magnesium Salts," Therapie, 53, 183, 1998, as per Applicant's IDS).

Laine-Cessac et al. teaches that the anticancer agent oxaliplatin induces neurotoxicity (1st sentence). This neurotoxicity can be dramatically improved by immediately treating patients undergoing oxaliplatin treatment with intravenous calcium gluconate (1g) and magnesium sulfate (1g). Laine-Cessac et al. also teach that the exact mechanism of oxaliplatin neurotoxicity is unknown, but that it is thought to be

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linked to either hypomagnesaemia or hypocalcaemia or both. A related platinum containing cancer treatment drug, cisplatin is known to produce renal magnesium wasting resulting in hypomagnesaemia, hypocalcaemia and hypokalaemia. It is also hypothesized that the oxaliplatin toxicity stems from the drug or its metabolites chelating calcium (2+) or magnesium (2+) cations.

Therefore, in view of the extensive rejection under 112 2nd paragraph above, Laine-Cessac et al. teaches a combination useful for sequential administration in anticancer therapy comprising oxaliplatin, injectable calcium, injectable magnesium as well as calcium in the oral form. Please note that there is nothing present in the injectable calcium formulation taught by Laine-Cessac et al. that would prevent one from taking it orally. Therefore the calcium gluconate of Laine-Cessac et al. meets the limitations of both an injectable and oral form of calcium. Please note also that the limitation "for administration both before and after oxaliplatin treatment" is a recitation of the intended use of the claimed combination. The intended use of a claimed invention must result in a structural difference between the claimed invention and prior art in order to patentably distinguish the claimed invention from the prior art. As the prior art compositions can be used in combination both before and after treatment with oxaliplatin, this limitation is met.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-6 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laine-Cessac et al. ("Acute Oxaliplatin Neurotoxicity Dramatically Improved with Intravenous Calcium and Magnesium Salts," *Therapie*, 53, 183, 1998).

The teachings of Laine-Cessac et al. are set forth above. With respect to claims 5 and 12, Laine-Cessac et al. fail to explicitly teach the concentrations of calcium and magnesium required by the claims, but rather teaches that 1 g of each calcium

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gluconate and magnesium sulfate are effective amounts. Furthermore, it is noted that the instant specification at paragraph [0030] states that an infusion containing 1 g of calcium gluconate and 1 g of magnesium sulfate before and after oxaliplatin gives good results.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to arrive at the claimed concentration between 8 and 20 mg/ml calcium ion and between 10 and 20 mg/ml magnesium ion, or more specifically 15 mg/ml magnesium ion, with a reasonable expectation of success based on the teachings of Laine-Cessac et al. One would have been motivated to do so because Laine-Cessac et al. teach the administration of 1g total of both magnesium sulfate and calcium gluconate via IV. The IV implies that the calcium and magnesium ions must be in solution and in order to achieve this amount and meet the claimed concentrations, one would merely need to select an IV volume of roughly 150 ml which is a completely reasonable and typical IV volume to inject, especially given the fact that both calcium gluconate and magnesium sulfate are highly soluble in water as is well known in the art. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, no more than routine experimentation would have been necessary to

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one of ordinary skill in the art to arrive at the claimed concentrations given that the total amount administered is taught by Laine-Cessac et al.

With respect to claims 6 and 11, Laine-Cessac et al. do not explicitly teach the administration of magnesium and calcium both prior to and after administration of oxaliplatin, but rather teaches the administration of calcium gluconate and magnesium sulfate immediately.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to administer calcium gluconate and magnesium sulfate both prior to and after administration of oxaliplatin given the teachings of Laine-Cessac et al. with a reasonable expectation that neurotoxicity will be inhibited or treated. One would have been motivated to do so because Laine-Cessac et al. teach that both calcium and magnesium ions have a neuroprotective effect when oxaliplatin is administered. One would have been especially motivated to administer calcium and magnesium before and after treatment with oxaliplatin because Laine-Cessac et al. teach that it is hypothesized that oxaliplatin and/or its metabolites chelate $\text{Ca}(2+)$ and $\text{Mg}(2+)$ ions. If one were to administer these ions before treatment, there would be an excess of them around and the neurotoxic effects due to Ca and Mg ions would be expected to be lessened. The same holds true for post treatment.

Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laine-Cessac et al. ("Acute Oxaliplatin Neurotoxicity Dramatically Improved with

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Intravenous Calcium and Magnesium Salts,” Therapie, 53, 183, 1998), in view of Chazard (US Patent Publication US 2002/0045632).

The teachings of Laine-Cessac et al. are set forth above. Laine-Cessac et al. do not teach the use of an oral calcium formulation nor the oral administration dosages or schedules required by the instant claims.

Chazard teaches the use of an oral formulation of calcium folinate to potentiate the coadministration of oxaliplatin in order to treat tumors (abstract, paragraph 36). Chazard teaches the calcium folinate is to be administered for 1-14 days ([0036]) at a dosage of 90 mg/day (see [0035]). More generically Chazard teaches that calcium folinate can be administered in an amount of 0.1 to 500 mg/kg/day ([0018]). Chazard also teaches an example (Example 2, [0033]-[0041]) calculating the maximal tolerated dose of oxaliplatin with calcium folinate ([0033]). Chazard teaches that 19 subjects ([0038]) were treated with up to 130 mg/m² of oxaliplatin while being treated with 90 mg/day of calcium folinate ([0035]) without experiencing dose limiting toxicity ([0038]). See the results of the decreased neurotoxicity in the table at paragraph [0040]. Note particularly the occurrences of paresthesia, and asthenia, two neurotoxic effects known to be attributed to oxaliplatin administration.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to supplement the IV administration of Ca and Mg before and after treatment with oxaliplatin with at least 1 g/day oral calcium and for 8 days after treatment with oxaliplatin given the combined teachings of the prior art with the reasonable expectation that doing so would decrease the occurrence and/or severity of

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the neurotoxic effects of oxaliplatin. One would have been motivated to do so because it is well known in the art that Ca and Mg injections help to ameliorate the neurotoxic effects of oxaliplatin and oral Ca is also known to ameliorate the neurotoxic effects of oxaliplatin. “It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) Therefore, one of skill in the art would have been imbued with the reasonable expectation that the combination of injectable Ca and Mg before and after oxaliplatin treatment and oral Ca after oxaliplatin treatment would result in decreased neurotoxicity derived from oxaliplatin administration. It is noted that 90 mg/day reasonably reads on at least 1 g/day. Furthermore, Chazard teaches that calcium folinate can be administered in an amount of 0.1 to 500 mg/kg/day. This amounts overlaps with the amount claimed. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, no more than routine experimentation would have been necessary to one of ordinary skill in the art to arrive at the claimed dosage amounts.

Response to Arguments

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Applicant's arguments filed 6/12/2009 in response to the rejection of claims have been fully considered, but are moot in light of the new grounds of rejection. However, in an effort to expedite prosecution, the examiner will address those issues still relevant to the current rejections.

Applicant argues that Chazard teaches that folinic acid is taught to potentiate the effect of fluorouracil, which in turn potentiates the effect of oxaliplatin. Thus although calcium is provided through calcium folinate, it is not taught to have any activity, therefore applicant concludes that the rejection is invalid.

This argument is not persuasive. The fact remains that calcium folinate is known to potentiate the effect of oxaliplatin and as also discussed in Chazard in the table at paragraph 40, neurotoxic effects of oxaliplatin are also reduced. It is noted that applicant's claims 6, 11, 13-14 do not specify the source of the calcium ions. Therefore calcium folinate is a valid source.

Applicant also argues that neither Chazard nor Laine-Cessac teach the administration of Mg and Ca before and after administration of oxaliplatin. It is noted, that this is the reason neither Chazard nor Laine-Cessac are used to reject the claims under the statute of anticipation. Rather these references are used to reject the claims under obviousness. It is obvious to administer Ca and Mg before and after oxaliplatin administration because as discussed in the above rejection. One would have been motivated to do so because Laine-Cessac et al. teach that both calcium and magnesium ions have a neuroprotective effect when oxaliplatin is administered. One would have been especially motivated to administer calcium and magnesium before and

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after treatment with oxaliplatin because Laine-Cessac et al. teach that it is hypothesized that oxaliplatin and/or its metabolites chelate $\text{Ca}(2+)$ and $\text{Mg}(2+)$ ions. If one were to administer these ions before treatment, there would be an excess of them around and the neurotoxic effects due to Ca and Mg ions would be expected to be lessened. The same holds true for post treatment. It is noted that applicant has not provided evidence of unexpected results to rebut this prima facie case of obviousness. It also needs to be addressed again that the recitation "useful for sequential administration in anticancer therapy" is found in the preamble of the claim. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). As addressed in the above extensive 112 2nd rejection of claim 1, claim 1 has been treated as if it were a kit, and therefore because the ingredients in the kit can be administered in any order, the preamble is met by the teachings of the prior art.

Applicant argues that because Chazard teaches the administration of 90 mg/day oral calcium that it cannot read on the claimed amount of at least 1g/day. However, this merely means the claim can be anticipated by this teaching. It does not prevent rejection of the claimed amount under the statute of obviousness. It is noted that Chazard also teaches from 0.1 to 500 mg/kg/day is an acceptable amount to administer of calcium folinate. The prima facie showing of obviousness regarding this amount has

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been set forth in the above rejection. Applicant has not provided unexpected results to rebut this case.

Applicant's submission off the official record of the Gamelin et al. reference has been noted. It is suggested that should applicant desire the reference to be fully considered, that it be officially submitted on the record on an IDS. It is noted that this reference does not teach the combination of injectable Ca and Mg with oral calcium folinate. It merely compares the differences between the Ca/Mg group and those receiving 5-fluoruracil and leucovorin (calcium folinate). Therefore it is not a comparison to the closet prior art. Furthermore the amount of calcium delivered in the form of calcium folinate is not the same as the amounts being claimed. The data in this reference is therefore not a comparison to the closest prior art, nor is it commensurate in the scope claimed.

Conclusion

Claims 1, 4-6, and 11-14 are rejected. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kortney Klinkel whose telephone number is (571)270-5239. The examiner can normally be reached on Monday-Friday 8am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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KLK

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611